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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/129,298	08/05/1998	CHARLES J. ARNTZEN	7991-023-999	4312

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EXAMINER

KRUSE, DAVID H

ART UNIT

PAPER NUMBER

1638

DATE MAILED: 03/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/129,298

Applicant(s)

ARNTZEN ET AL.

Examiner

David H Kruse

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 06 June 2001 and 28 June 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-4 and 8-27 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4 and 8-27 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Status of the Application***

1. This Office Action is in response to the Reply filed 6 June 2001 and the Supplemental Reply filed 28 June 2001.
2. The declaration by Dr. Peter Beetham (Beetham Declaration) filed 6 June 2001 and by Richard A. Metz (Metz Declaration) filed 28 June 2001 have been entered into the file. Both declarations have been considered and are discussed below. In addition, the declaration by Keith Allen Walker (Walker Declaration) filed 29 December 1999 has been considered.
3. Claims 1-4 and 8-27 are pending.
4. The rejection of claims 1-4 and 8-27 under 35 U.S.C. § 103 as being obvious over Kmiec (US Patent 5,565,350) in view of Kmiec (US Patent 5,731,181) and Stanford (US Patent 5,204,253) is withdrawn in view of Applicant's arguments in relation to the Stanford reference only.
5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Claim Rejections - 35 USC § 112***

6. Claims 2, 8, 17, 19 and 20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the acronym "MDON" appears to be Applicant's own descriptor for "Mixed Duplex Oligonucleotides" and was not an art recognized synonym for a "Chimeric Mutational Vector" as described

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by Kmiec in U.S. Patent 5,731,181. It is suggested that at claim 2 the term "MDON" be replaced with the phrase -- Mixed Duplex Oligonucleotides (MDON) -- to clarify the metes and bounds of the claimed invention.

7. Claims 1-4 and 8-27 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of making a localized mutation in a target plant ALS gene or a transgenic GFP gene *in situ* in a plant cell, does not reasonably provide enablement for a method of making a localized mutation in any target gene in a plant cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant claims a method of making a localized mutation causing a desired trait in a target gene in a plant cell using a recombinagenic oligonucleobases comprising adhering to a particle a recombinagenic oligonucleobase, wherein said adhering step is performed in a solution comprising 1.1-1.4 m NaCl.

Applicant teaches a method of making a localized mutation in a plant ALS gene *in situ* in a plant cell and making a localized mutation in a GFP transgene *in situ* in a plant cell using  $\text{CaCl}_2$  (pages 21-26 of the Specification).

Applicant does not teach a method of making localized mutations in other genes *in situ* in a plant cell or using other salts.

*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations for determining whether or not undue experimentation would be necessary to practice an invention. These factors are: the quantity of experimentation

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necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Applicant has provided limited guidance for a method of making a localized mutation causing a desired trait in a target gene in a plant cell as broadly claimed. The instant invention employs the general teachings of Kmiec, which Applicant acknowledges in section 2.1 on pages 1-2 of the specification. While the teachings of Kmiec are generally applicable to the instant invention, the nature of the art at the time of Applicant's invention shows that the Kmiec method had not been widely applicable in plants, requiring one of skill in the art to perform empiric experimentation in order to perfect the use of the Kmiec method in plant cells. The art teaches that application of the Kemic method in plants is unpredictable because the mismatch repair system in plants appears to operate differently than the mismatch repair system in mammalian cells, as exemplified by Kmiec (see Hohn and Puchta 1999, Proc. Natl. Acad. Sci. USA 96:8321-8323, especially the paragraph spanning the columns on page 8322). In fact, the art teaches that some recombinagenic oligonucleobases (syn. chimeric oligonucleotides, COs) do not produced the intended mutation in the target gene in a plant cell. Hence, it would have required undue trial and error experimentation by one of skill in the art at the time of Applicant's invention to determine all of the desired localized mutations causing a desired trait in a target gene in a plant cell, design a myriad of recombinagenic oligonucleobases and modify a myriad of plants in order to

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determine which combination of target gene, recombinagenic oligonucleobase and plant would produce a localized mutation causing a desired trait in a target gene in a plant cell as broadly claimed.

The Walker Declaration (1999) argues that it would not require undue trial and error experimentation to screen for other mutations that lead to a desired phenotype because one of skill in the art could use available resources, even though they be labor intensive, to select for the desired trait (pages 3 and 4 of the Walker Declaration). The Examiner responds, although labor intensive screening would not constitute undue experimentation, it is the very nature of the invention related to selecting targets in known genes, designing recombinagenic oligonucleobases such as MDONs and screening through a myriad of MDONs and modified plants in order to practice the claimed invention within the breadth of the claims that would lead to undue trial and error experimentation.

Finally, at claim 8 it would have required undue experimentation to evaluate other, non-exemplified method limitations such as salts that would have been required to practice Applicant's invention.

### ***Claim Rejections - 35 USC § 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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9. Claims 1 and 16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Svab *et al* 1990 (Proc. Natl. Acad. Sci. USA 87:8526-8530).

Svab discloses a method for making a localized mutation in a target gene in a plant cell comprising adhering to a particle a recombinagenic oligonucleobase having a sequence identical to the sequence of interest having at least 6 base pairs to both the first and second fragment of the target gene and an intervening region which contains at least 1 nucleobase heterologous to the target gene (a wild-type 16S gene with mutant codons embedded therein), introducing the particle into a cell of a population of plant cells and identifying a cell of the population having a mutation located between the first and second fragments of the target gene (see the ABSTRACT and MATERIALS AND METHODS on pages 8526-8527). Hence, Svab has previously disclosed all of the claim limitations.

***Claim Rejections - 35 USC § 103***

10. Claims 1-4 and 8-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kmiec (U.S. Patent 5,731,181, filed 17 June 1996) in view of Dunder *et al* (in Gene Transfer To Plants 1995, Potrykus and Spangenberg, Eds., Springer Verlag publisher, Chapter 15, pages 127-138) and in view of Applicant's admission.

Kmiec teaches a method of introducing an alteration in a target sequence of the genome of a plant cell comprising providing a recombinagenic oligonucleobase (Claims 30-32).

Kmiec does not specifically teach a method comprising adhering a recombinagenic oligonucleobase to a particle and introducing said particle into a cell of

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a population of plant cells. Kmiec does not teach a method wherein a recombinagenic oligonucleobase is adhered to a particle in a solution comprising 1.1-1.4 m NaCl and 18-22  $\mu$ M spermidine and at least 14  $\mu$ g/ml MDON. Kmiec does not teach a method wherein the target gene is from the group listed in Applicant's claims 9, 12, 21 and 24 or wherein the plant is maize, wheat, rice, lettuce, potato, tomato, canola, soybean or cotton.

Dunder teaches a method of biolistic transformation of plant cells comprising adhering an oligonucleobase to a gold particle comprising  $\text{CaCl}_2$  and spermidine, and transformed cells (see pages 134-135).

Applicant admits that the genes listed in claims 9, 12, 21 and 24 and that methods of transforming maize, wheat, rice, lettuce, potato, tomato, canola, soybean or cotton were known in the art at the time of Applicant's invention (pages 8-9 and 12-20 of the specification).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicant's invention to modify the method of Kmiec using the teachings of Dunder to modify a target gene in a plant cell. In addition, it would have been obvious to use the method of Kmiec modified using the teachings of Dunder to modify specific genes in a plant cell known in the art at the time of Applicant's invention. One of skill in the art would have had a reasonable expectation of success given the success of Kmiec in producing a localized mutation causing a desired trait in a target gene.

Both the Beetham Declaration and the Metz Declaration argue that the critical step in the claimed method is adherence of the recombinagenic oligonucleobase to a



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particle. The Examiner responds that adherence of an oligonucleobase to a particle using a salt such as calcium chloride and spermidine appears to be a standard method well known in the art at the time of Applicant's invention. If the limitations at claim 8 are critical to the teachings of unexpected results in the instant invention, then these limitations should be incorporated into the independent claims. Without incorporation of the limitations of claim 8 into the independent claims, the specific concentrations of salt, spermidine and oligonucleobase would have been obvious to one of skill in the art as representing simple experimental variations not critical limitations.

**Conclusion**

11. No claims are allowed.
12. This Office Action is non-final.
13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David H. Kruse, Ph.D. whose telephone number is (703) 306-4539. The examiner can normally be reached on Monday to Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy Nelson can be reached at (703) 306-3218. The fax telephone number for this Group is (703) 872-9306 Before Final or (703) 872-9307 After Final.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Kim Davis whose telephone number is (703) 305-3015.

DAVID T. FOX  
PRIMARY EXAMINER  
GROUP 130

David H. Kruse, Ph.D.  
21 February 2002

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